REMARKS

Applicant has amended the claims to make explicit that which was implicit. Claim 1 specifies that the "whole gene" is the gene from the 5' to 3' end and can be the coding region (see, e.g., page 5, paragraph 10, and claim 4) or the genomic gene (see, e.g., page 5, paragraph 10, page 25, paragraph 90, and claim 5). Claim 2 has been amended to correct a typographical error, to indicate the intended dependency of this claim on claim 1, rather than claim 10 as originally filed. Claims 4 and 5 have editorial changes to conform to the amendment to claim 1. Claims 6, 9, and 10 have been editorially amended. As such, these amendments do not introduce new matter and their entry is respectfully requested. Claims 2 – 10 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the present invention.

Applicant respectfully submit that the above-described amendments to the claims have obviated this rejection.

Accordingly, applicant respectfully submits that all claims comply with 35 U.S.C. § 112, second paragraph and that this rejection should be withdrawn.

Claims 1 – 4 and 11 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Modrich et al. (U.S. 5,459,039) in view of Wodicka et al. (Nature Biotech. Vol. 15, 1997).

Applicants respectfully submit that this rejection be withdrawn for the following reasons.

The present invention is directed to the use of DNA chip technology to scan for and detect mutations (including allelic differences) in a complex target that at a minimum spans 10 different genes. For example, claim 1 is specifically directed to using a scanning array to scan at least ten different genes. Previous technologies to scan for polymorphisms and mutations have been restricted to looking at mutations in specific genes. Typically they did not even look at the

entire gene. However, the prior art fails to teach or suggest how to detect *unknown* mutations in a *population* of several genes. In the applicant's invention, instead of selecting a single gene at a time and examining whether it contains mutations, the first step is to scan a large sequence of DNA (at least 10 genes), however complex, to identify and isolate mismatch-containing (i.e. mutation-containing) DNA fragments. Thus, one identifies the relevant sequences in and then determines which genes these DNA fragments belong to, by using DNA arrays. Accordingly, the present invention adopts an entirely different approach from the prior art and results in a means to look at complex targets.

The Examiner admits that Modrich does not teach the use of an array to identify the gene containing the mismatch. However, the difference between Modrich and the present invention is even more fundamental. For example, Modrich, starts with a single known gene and looks for the presence of any mutations. In contrast, the present invention does not require knowing the identify of the gene containing the mismatch. Second, the present invention is not limited to looking at one target DNA at a time. Rather, it is directed to looking at multiple genes. Third, the present invention takes advantage of DNA chip technology, unlike Modrich. Thus, Modrich does not teach or suggest the use of DNA chip technology to scan for multiple mutations simultaneously.

The Examiner has cited Wodicka as disclosing a DNA chip array representing the yeast genome to overcome the deficiency of Modrich. However, the DNA chip of Wodicka is primarily directed to analysis of gene expression and assessing genetic differences between different strains, including detecting for example chromosomal deletions, duplications, and loss of heterozygosity. Wodicka in no way teaches a method of detecting a mutation such as a single nucleotide polypmorphism, as is possible with the present invention. Further, nothing in

Wodicka discusses the use of such an array to detect the presence of a mutation, including the use of mismatches to do so.

In combining Modrich and Wodicka to argue that the present invention is obvious, the Examiner is using impermissible hindsight reconstruction. The Examiner cannot pick and choose references when considering the prior art. Instead, the entire invention must be considered in light of the state of the art that must be considered. Considering the applicant's invention as a whole, there is nothing that would provide the skilled artisan any motivation to combine the Modrich method for mismatch detection with the general DNA chip array of Wodicka. Moreover, there would be no such motivation because when using a gene expression assay one does not need to look at the entire gene from the 5' to the 3' end. As explained at pages 2 and 3, gene expression assays are typically biased to looking at the 3' end. But even when not so biased they have no need to insure binding to an entire gene to determine if there is gene expression. Certainly, there would be no basis to look at an intron (see, e.g., claim 5). Thus, there would be no motivation to take the different approach of Modrich, looking for specific mutations used, and combine it with the gene expression array of Wodicka. Wodicka explicitly acknowledged at page 1361 that not all the oligonucleotide probes used hybridized with equal affinity and specificity. Then went on to state that this was not a problem. This is because Wodicka was only looking at expression.

This lack of motivation is apparent given the number of DNA chips and bioinformatics applications and the absence of such a suggestion. Molecular biology and molecular medicine have been dominated for the last 5 – 10 years by the emergence of technologies to analyze highly complex representations of DNAs and other nucleic acids. This explosion of interest in part has been fueled by the rapid increase in the availability of sequence information, including the

sequencing of the entire genomes of many organisms including man. Yet there is no suggestion to convert a gene expression DNA assay to a mutation scanning array.

Claims 5 and 6 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Modrich et al. (U.S. 5,459,039) in view of Wodicka et al. (Nature Biotech. Vol. 15, 1997), and further in view of Beutler (U.S. 5,266,459). Applicants respectfully disagree for the following reasons.

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All that Beutler teaches is that mutations can occur in introns. The Examiner uses this disclosure to argue that it would have been obvious to include non-coding regions of a gene in a mutation scanning array. However, for all of the reasons stated above, the combination of Modrich and Wodicka would not teach a mutation scanning array to the skilled artisan, and Beutler adds nothing to cure this fundamental defect. Accordingly, the combination of references does not render the present invention obvious.

Claims 6 – 10 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Modrich et al. (U.S. 5,459,039) in view of Wodicka et al. (Nature Biotech. Vol. 15, 1997), and further in view of Cronin (WO 98/30883). Applicants respectfully disagree for the following reasons.

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Cronin merely teaches that mutations can be searched for and identified in reference sequences, including genes for many specific disease conditions. However, for all of the reasons stated above, the combination of Modrich and Wodicka would not teach a mutation scanning array to the skilled artisan, and Cronin adds nothing to cure this fundamental defect. Accordingly, the combination of references does not render the present invention obvious.

Claims 1 – 13 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 – 30 of U.S. Patent No. 6,174,680.

On or before the Examiner's indication that these claims contain allowable subject matter, applicants will file a Terminal Disclaimer with respect to this rejection, thereby obviating it.

In view of the foregoing, applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

Respectfully submitted,

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